In This Issue

Molecular Scenes from the Biofilm

PAGE 1503

Biofilm formation is an important bacterial virulence mechanism involved in a series of infectious diseases. Joo and Otto review mechanisms of in vivo biofilm formation and include discussion of a shifting view of quorum-sensing in biofilm infection and its use as an antibiofilm drug development target.

Putting a Stop to Skp2-Mediated p27 Degradation

PAGE 1515

Multiprotein SCF E3 ligase enzymes is a mediator used by cancer cells to evade growth control checkpoints. By using a combination of tools, Wu et al. identified a set of compounds that target a bipartite protein interface formed by SCF proteins Skp2 and Cks1 and interfere with the p27 degradation pathway.

Claisen Cyclase and Deacetylase Packed into One Enzyme

PAGE 1525

Vagstad et al. clarify an efficient single enzyme biosynthetic route to the key melanin intermediate tetrahydroxynaphthalene (THN). Pks1 generates a typical monocyclic enzyme-bound precursor but unusually has a TE domain that catalyzes both Claisen cyclization and deacetylation reactions to generate THN directly.

Punching the Plasmodial Proteasome

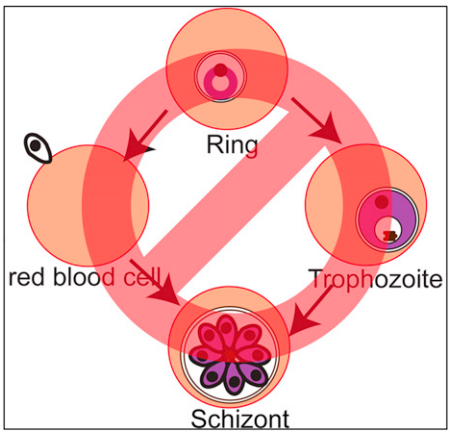
PAGE 1535

The *Plasmodium* proteasome has been suggested, albeit not validated, to be a potential antimalarial drug target. Li et al report a screen of a focused library and identify one compound, PR3, that targets the *Plasmodium* proteasome, has parasite killing activity in vitro, and reduced toxicity in host cells.

Getting at Plasmodial Vacuole

PAGE 1546

Falcipains, a family of cysteine proteases from *Plasmodium falciparum*, have been identified by Stolze et al. as direct targets of the potent antimalarial natural product Symplostatin 4. Symplostatin 4 treatment decreases parasitemia, and the level of inhibition relies on its unique structural arrangement.



Inhibitors of Mtb Malate Synthase

PAGE 1556

The glyoxylate shunt is vital for survival of Mycobacterium tuberculosis (Mtb) inside the host. Krieger et al. report the development of phenyldiketo acid inhibitors of Mtb malate synthase, one of two glyoxylate shunt enzymes, which are active against Mtb grown in culture and in a mouse model of tuberculosis.

Helping in the Times of Need

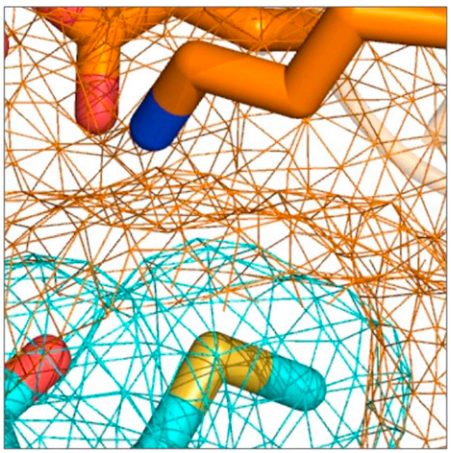
PAGE 1568

When starved for iron, *Staphylococcus aureus* limits the amount of cellular citrate, a paradox given that siderophores used to acquire iron contain citrate. Cheung et al. uncover an enzyme that synthesizes citrate for siderophore production irrespective of the metabolic status of the cell to help *S. aureus* cope.

Erecting HIV-1 Road Block

PAGE 1579

CCR5, the major HIV-1 coreceptor, is a primary target for HIV-1 entry inhibition. CCL5/RANTES, a natural CCR5 ligand, is among the most potent HIV-1 blockers. Secchi et al. present work on enhancing HIV-1 blocking activity of the parent peptide to produce leads for more effective HIV-1 inhibitors.



Structure of Amidotransferase Bienzyme

PAGE 1589

Glutamine amidotransferases and synthases act to incorporate nitrogen into metabolites by using reactive ammonia generated from glutamine. List et al. report the structure of an amidotransferase bound to glutamine and show that the ammonia pathway towards the synthase active site is blocked and the two sites are uncoupled.

Random Codons for Chemical Space Exploration

PAGE 1600

Young et al. use codon randomization coupled with colony-level high throughput MALDI-TOF screening to exhaustively explore chemical space throughout the GE37468 thiopeptide. The method yielded insights into thiopeptide maturation as well as SAR for thiopeptide antibiotics active against MRSA.

Terpendole E's Cameo Appearance

PAGE 1611

Terpendole E, an indole-diterpene compound, is a natural product inhibitor of kinesin Eg5. Motoyama et al. analyze the terpendole biosynthetic gene cluster and show that terpendole E is a key early intermediate in terpendole biosynthesis, explaining its transient appearance.

Cell Morphology Encyclopedia Helps Find the Target

PAGE 1620

Visual observation is a powerful approach for screening drug candidates. Futamura et al. focus on intact cell images and develop a faster way to unravel the mode of action of investigative compounds based on Morphobase, an encyclopedia of cancer cell morphologies induced by hundreds of reference compounds.